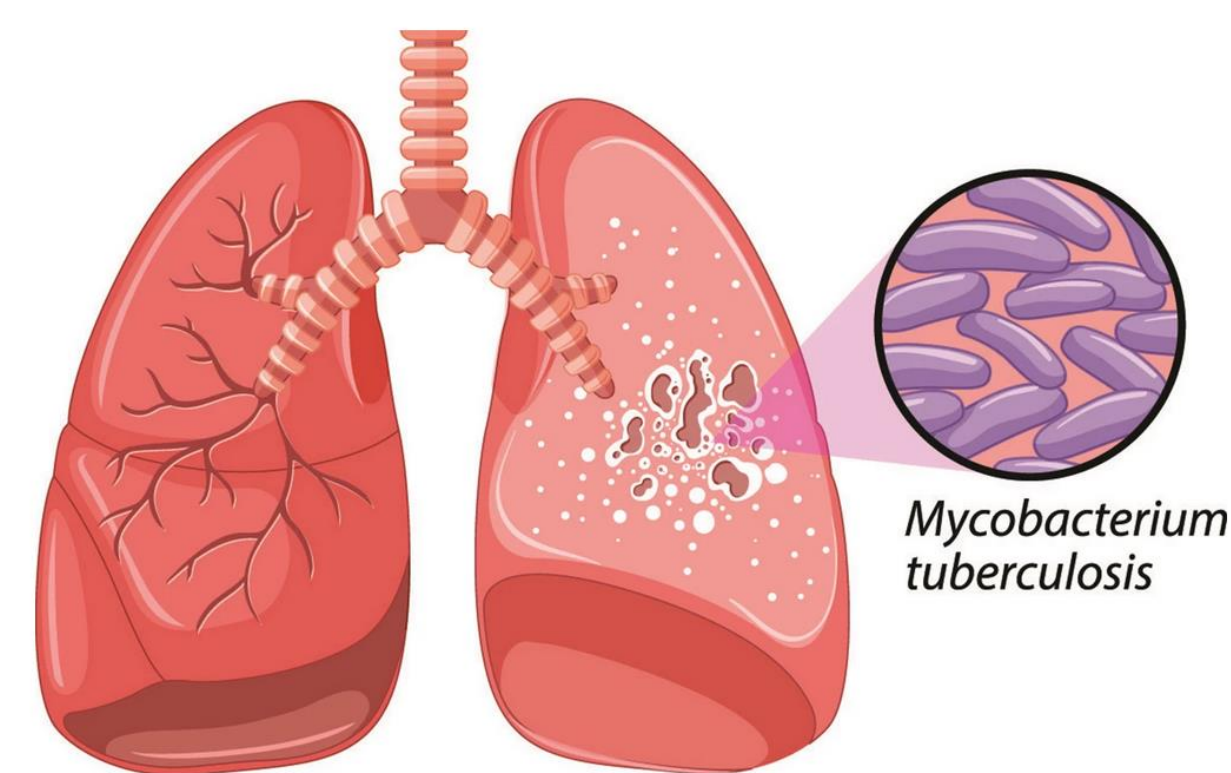


# Drug-Induced Livery Injury Associated with Antitubercular Medications

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## Introduction

Tuberculosis (TB) is a globally concerning and infectious disease resulting in over 4000 deaths daily. It is caused by the bacteria, *Mycobacterium tuberculosis*, and has infected close to a quarter of the world's population. Treatment involves taking a regimen of antibiotics that include isoniazid, rifampin, pyrazinamide, and ethambutol. Like many medications, however, side effects exist. Drug-induced liver injury (DILI), also known as drug-induced hepatotoxicity, is a toxicity imposed on the liver from prescription or over-the-counter medications. Antitubercular medications used to treat active TB have been linked to liver injury and overall treatment failure in about 28% of cases. Severe cases have resulted in patients unable to recover from the injury after discontinuation of the medications, leading to liver transplantation or death.



**Risk Factors:** Excessive alcohol consumption, dietary or herbal substances, malnutrition, HIV co-infection, elevated baseline aminotransferase levels



Figure 1. First-line Antitubercular medications

## Objective

The goal of this literature review aimed to described the correlation between antitubercular medications and drug-induced liver injury by understanding the mechanism of action of the drugs in addition to their mechanism of injury towards the liver.

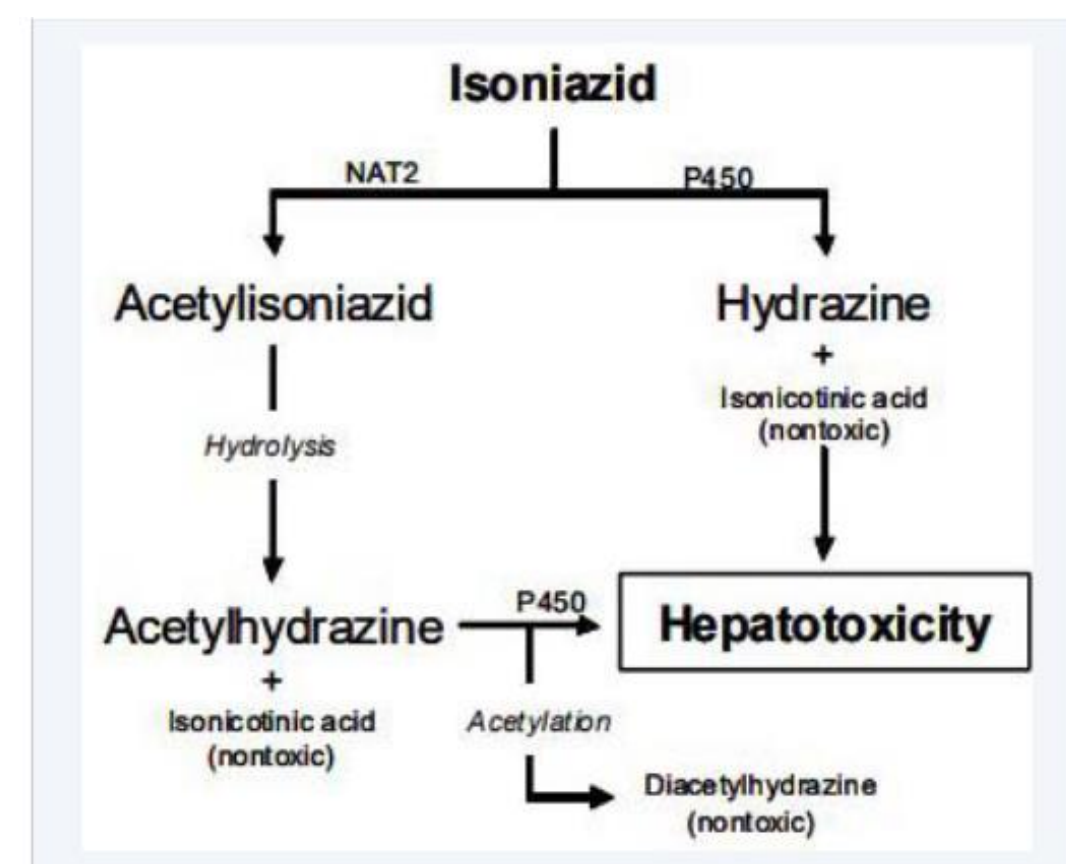


Figure 2. Isoniazid mechanism of liver injury. Formation of acetylhydrazine and hydrazine result in oxidative stress and induce CYP2E1, which increases toxic metabolic intermediates.

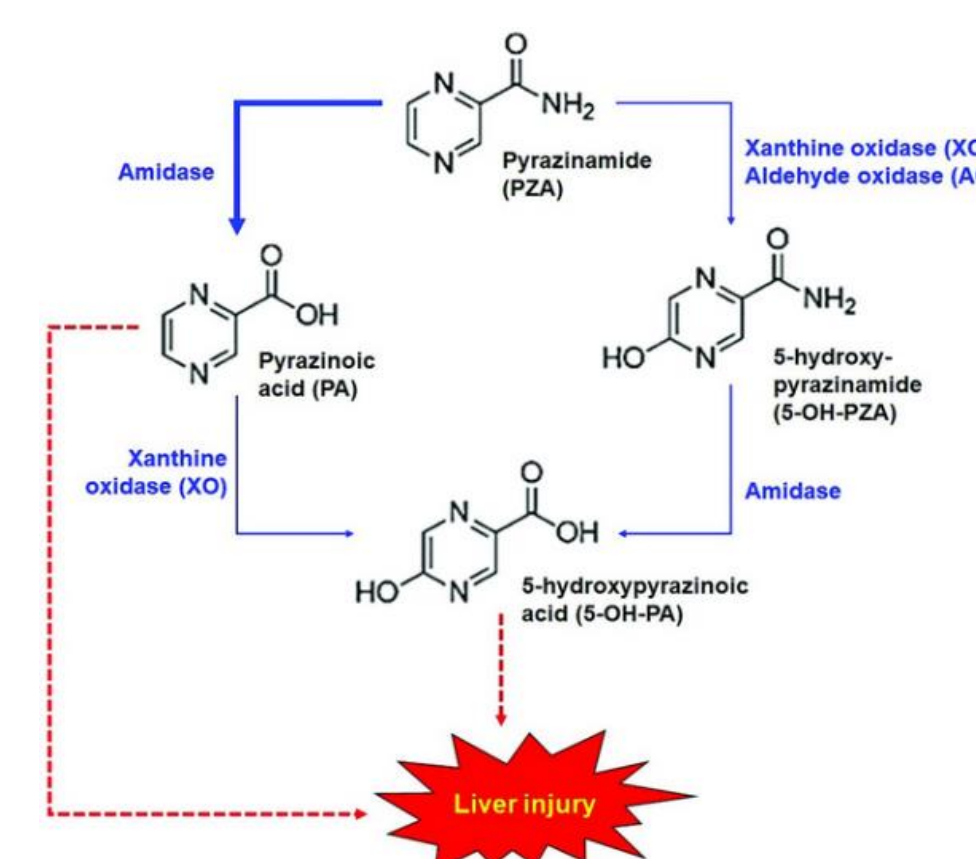


Figure 3. Pyrazinamide mechanism of liver injury. Metabolic intermediates pyrazinoic acid and 5-OH-PZA are proposed to be the result of hepatotoxicity.

## Conclusion

- DILI is difficult to diagnose because many factors can result in liver disease and patients may often be asymptomatic, therefore, other common causes of liver injury are first ruled out prior to considering a diagnosis of DILI
- First-line regimen of antibiotics used to treat TB (isoniazid, pyrazinamide, rifampin and ethambutol) are highly effective but have a significant potential of inducing hepatotoxicity
- Reliable lab testing doesn't exist in predicting whether drugs have the potential to induce liver injury, but Hy's law has become the standard guideline in determining the likelihood a drug will result in liver injury
- Studies have proposed the overall mechanism of toxicity on the liver from antitubercular medications is the result of their metabolic byproducts during metabolism with an increased risk of liver injury in those with genetically slow acetylation rates specifically in those taking isoniazid and an overall risk in those with long-term use of antitubercular medications

**Patient Education:** Taking over-the-counter herbal or dietary supplements while taking meds for TB can increase the risk of developing liver injury. Most supplements lack safety assessments and are not regulated by the FDA therefore their efficacy cannot be ensured. Cases involving liver injury and supplements have been growing and physicians need to be made aware by their patients if taking any supplements to help reduce the risk of developing liver injury. The only treatment in place for drug-induced liver injury involves early diagnosis and immediate discontinuation of the medication, therefore, frequent screening and monitoring remains important to help minimize the risk.

**Future Direction:** Treatment options to combat drug-induced liver injury have yet to be discovered. Diagnosis and prevention remain challenging since the mechanism of action of meds such as ethambutol and pyrazinamide are not well-understood. Prioritizing the production of new antitubercular medications that can be administered through different routes thus avoiding the liver should be considered. Research on developing medications with hepatoprotective properties should also be prioritized.

## Hy's Law (FDA's approach to liver safety assessment for new drugs)

1. Serum alanine aminotransferase or aspartate aminotransferase levels are greater than three times the upper limit normal (ULN)
2. Increased serum total bilirubin is greater than two times ULN with no findings of cholestasis .
3. No other reason can be found to explain the combination of increased aminotransferase and total bilirubin levels, such as viral hepatitis, liver disease, or another drug capable of causing liver injury.

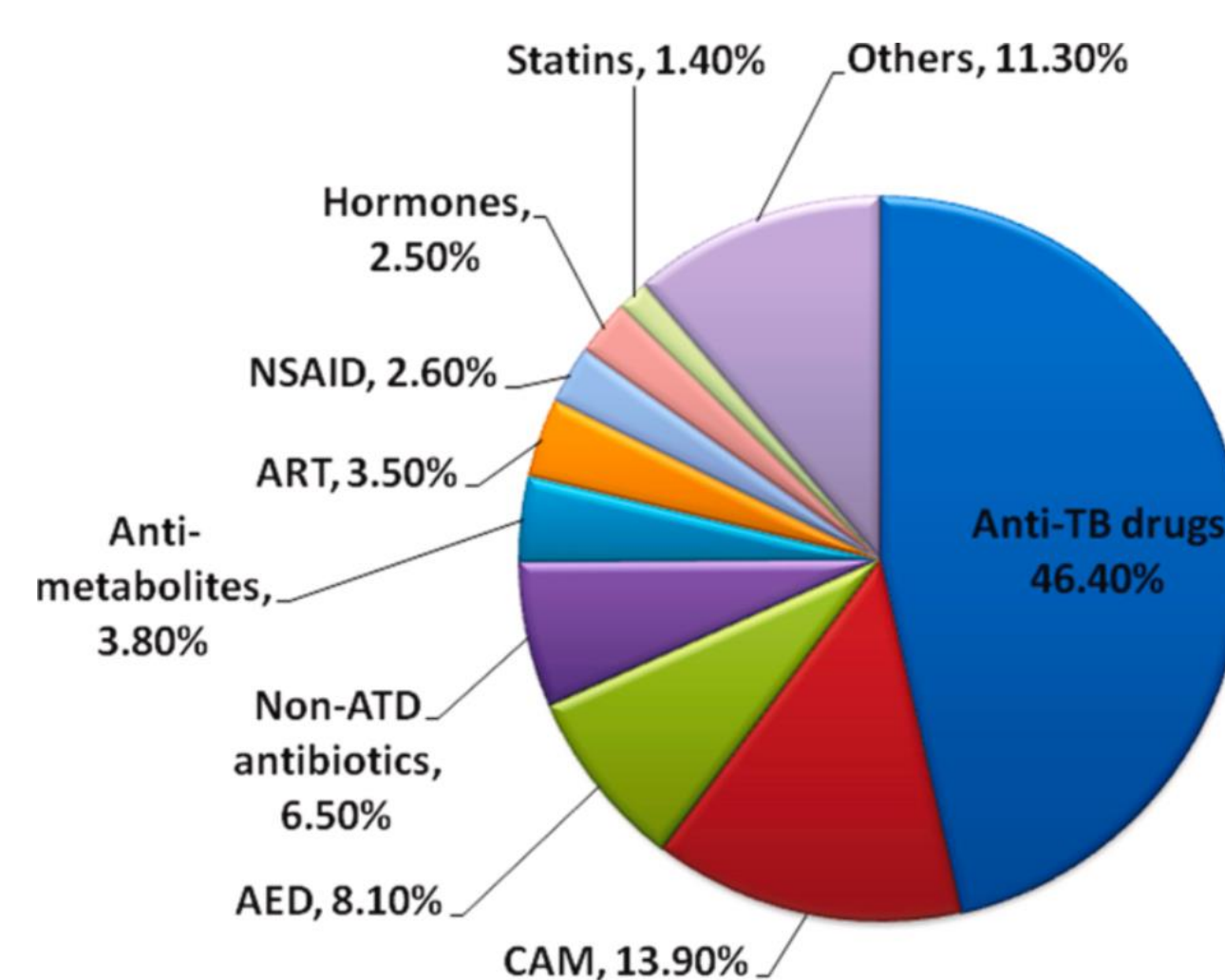


Figure 4. Medication agents/classes known to induce liver injury

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